Editorial

Echocardiographic Detection of Heart Transplant Graft Dysfunction
A New Twist on an Old Theme

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It would have seemed that the problem is relatively simple: graft rejection or coronary artery disease after cardiac transplantation induces edema, inflammation, myocyte damage, necrosis, ischemia, and sometimes fibrosis, resulting in ventricular systolic and diastolic dysfunction. These should be detectable by echocardiography; yet, the quest for a sufficiently sensitive, specific, and conclusive echo marker of orthotopic heart transplant (OHT) graft dysfunction has been elusive. Consequently, children with OHT may undergo repeated myocardial biopsies and coronary angiography to diagnose graft rejection and coronary artery disease. Although these procedures are associated with low risk overall, they are not without complications and entail considerable discomfort, especially in children, and may be performed repeatedly over the course of many years. Thus, it would be of substantial benefit to have an echo measure that can be applied simply and repeatedly to diagnose or exclude acute or chronic graft dysfunction.

Multiple echo measures have been proposed to address this need. These have included a change in chamber dimensions or wall thickness to indicate ventricular remodeling or edema, ejection phase measures, such as ejection fraction or fractional shortening, development of pericardial effusion, and more recently tissue Doppler and myocardial deformation to more directly assess impaired myocardial function, which underlies graft dysfunction. Impaired myocardial relaxation and increased stiffness induced by graft rejection or coronary artery disease may precede systolic dysfunction. Therefore, diastolic measures, such as the $E/A$ ratio, tissue Doppler $e'$, and $E/e'$ ratio, may be early markers of graft dysfunction. Interestingly, some pediatric studies have found right ventricular (RV) parameters to be more sensitive than left ventricular (LV) parameters. In addition, our group and others have used provocative testing in children with OHT to detect wall motion abnormalities that may herald coronary artery disease, initially with dobutamine stress echocardiography and, more recently, with exercise echocardiography in children of appropriate age. Moreover, assessing functional reserve through exercise echo may unveil graft dysfunction.

The European Association of Cardiovascular Imaging (EACVI) has recently produced an extensive document on cardiac imaging to assess and follow adult patients after OHT. They recommend mandatory reporting of multiple echocardiographic indices, including (among others) LV end-diastolic and end-systolic volumes, ejection fraction, septal and infero-lateral wall thicknesses, assessment of valvar regurgitation, $E$, $A$, and pulmonary vein Doppler flow velocities, left atrial volume, mitral $s'$ and $e'$ wave tissue Doppler velocities, global longitudinal strain, pericardial effusion, and measures of RV function, including wall thickness, tricuspid annular systolic excursion, fractional area change, $s'$ tissue velocity, and longitudinal strain. Optional measurements include 3D echocardiography and the myocardial performance index.

It is fitting that the EACVI guideline lists LV and RV longitudinal strain as mandatory because LV ejection fraction is a late indicator of graft dysfunction and may not correlate with the grade of rejection. The myocardial injury associated with graft rejection or ischemia seems well suited to deformation imaging, in that strain directly interrogates myocardial function. Lack of improvement in strain early after heart transplant and low LV global longitudinal strain on follow-up have been associated with poor outcomes. Recently, diastolic strain parameters have been found to detect changes in LV filling pressures that may herald graft dysfunction in pediatric OHT recipients.

Although the comprehensive EACVI guideline highlights assessment of longitudinal strain to detect graft dysfunction, rotational mechanics are not discussed or recommended and make only a cursory appearance as a single reference in passing. In this issue of Circulation: Cardiovascular Imaging, Nawaytou et al report on left ventricular rotational mechanics in children after heart transplantation. This prospective study aimed to determine the characteristics of LV rotation in children after OHT at rest and during exercise. Their investigation is rooted in adult heart transplant studies that found altered LV torsion (defined as the difference between apical and basal rotation (twist) corrected for LV length) during graft rejection and transplant associated coronary artery vasculopathy. The final cohort included 32 children with OHT, without evidence for active rejection or coronary artery vasculopathy, and 35 age- and sex-matched controls. Subjects >8

See Article by Nawaytou et al

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years of age performed moderate-intensity exercise through repeated straight leg raises to increase the heart rate by 20 to 30 bpm (n=13 OHT subjects). Rotation mechanics were analyzed at rest and after moderate exercise from LV short-axis and apical 4-chamber views, using vendor-independent software speckle-tracking analysis of echocardiography Digital Imaging and Communications in Medicine clips. The study found that torsion and untwist rate were significantly higher in OHT recipients compared with control subjects and that OHT recipients were unable to increase torsion with exercise. Based on earlier studies, and on the assumption that torsion reflects radial force and that displacement reflects volume change, the authors computed a torsion versus radial displacement loop using the speckle-tracking echo data (similar to the pressure–volume relationship used to characterize ventricular function). They found that the slope of the systolic limb of the torsion–radial displacement loop (thought to reflect potential energy created during systole) was increased at baseline versus control subjects, but that this measure decreased with exercise in the majority of OHT patients. They conclude that the slope of the torsion–radial displacement loop, and its response to exercise, may serve as a marker of OHT graft dysfunction.

Given the multitude of existing echo parameters to detect graft dysfunction, what is the contribution of the study by Nawaytou et al? Several potential contributions are apparent: (1) subjects were prospectively recruited, presumably improving image and data quality and consistency; (2) echo-derived LV mechanics were used to approximate force–volume relations; and (3) exercise-echo was used to evaluate myocardial functional reserve.

Adding volume assessment to LV mechanics to construct a correlate of the force–volume relationship may add valuable functional data; and the area subtended by the force (or pressure)–volume loop reflects ventricular work. These indices, albeit coarse when assessed noninvasively, are relatively available through assessment of LV mechanics, even at the bedside. Using similar principles, and building on our prior catheter-based study, we recently proposed this concept to noninvasively assess RV longitudinal work (in contrast to the LV radial vector used by Nawaytou et al) using the product of tricuspid annular systolic excursion, as the displacement surrogate for volume, and RV pressure, estimated from tricuspid regurgitation. These simple but more comprehensive echocardiographic surrogates of ventricular function and work will hopefully yield more sensitive and better indices of ventricular dysfunction as proposed by Nawaytou et al in the current article.

LV strain, especially global longitudinal strain, is increasingly used in clinical practice and is recommended by the American Society of Echocardiography guidelines for evaluation of LV function in adults and in the aforementioned EACVI guidelines for evaluation of OHT. In contrast, rotational mechanics, including torsion, are infrequently used in clinical practice and are not recommended in current guidelines. Because graft dysfunction affects both systolic and diastolic performance, the use of rotation mechanics is attractive because it incorporates both systolic (twist and its derivatives) and diastolic (untwist) components and their coupling. Assessment of twist automatically evaluates untwist; and twist–untwist mechanics reflect systolic–diastolic coupling, in that potential energy accumulated during twisting is used during untwisting to promote diastolic filling. Using tissue Doppler, we recently proposed that impaired systolic–diastolic coupling may contribute to ventricular dysfunction in children with dilated cardiomyopathy. Thus, the torsion–displacement loop is expected to assess systolic–diastolic coupling, but interestingly in the article by Nawaytou et al, only the systolic, and not the diastolic, limb was different between patients and controls. It is noteworthy that assessment of rotation mechanics in OHT patients was published some 25 years ago, and intriguingly one of these studies embedded tantalum markers in the graft myocardium. This gold standard methodology found alterations in diastolic untwist mechanics, rather than the systolic differences found by Nawaytou et al. Thus, it is still uncertain which component of torsion is affected by graft dysfunction, and this requires further investigation. In addition, the question arises that if rotation mechanics have been recognized for over 2 decades in OHT and if noninvasive technology has evolved during this time to make measurements more accessible, why is it not used more widely? This question is true of rotation mechanics in the assessment of LV dysfunction, in general, beyond transplant medicine.

Exercise echo to detect wall motion abnormalities is often used in adult patients and is directly germane in OHT patients to detect coronary artery disease. Assessment of functional reserve and the force–frequency relationship during exercise are less regularly performed but are important facets of cardiac function. Nawaytou et al enhance the power of rotation mechanics and ventricular work by assessing the response to exercise. Our group has been interested in functional reserve in transplant patients, using exercise echo to assess the force–frequency relationship through tissue Doppler and strain imaging. Whether measures of ventricular work, such as the torsion–displacement relationship, will be useful to depict functional reserve is suggested in the article by Nawaytou et al, but remains to be definitively demonstrated; it remains to be seen how reliably these depict force–frequency relationships. Indeed, inspection of Nawaytou’s data shows that the change in the systolic slope of the torsion–displacement relationship is largely related to the baseline condition. Subjects with a low slope at baseline increased the slope with exercise and those with a high slope at baseline decreased with exercise. This may reflect a regression to the mean phenomenon more than dysfunction during exercise per se, and caution is warranted when interpreting the results and the authors’ conclusions. There are additional points in the paper that warrant attention. For example, it is notable that the $e'$ was lower and $E/e'$ ratio significantly higher in OHT patients versus controls. Likewise, longitudinal strain trended toward being lower in the OHT group. These measures are simpler to apply than rotational imaging or the torsion–displacement loop and have been found to predict cardiac graft dysfunction in other studies. Therefore, the incremental benefit of torsion imaging in detecting graft dysfunction is still undetermined. Additionally, the article does not explore the relationship of the torsion–displacement loop to other functional measures; this is important when moving toward implementation in clinical practice. The exercise
protocol used in the study was not strictly standardized and elicited submaximal effort. Likewise, the article’s conclusions are largely based on a statistically significant difference between subjects and controls for only one of several indices studied in a relatively small subgroup of the cohort. Therefore, a type 1 statistical error may exist. Moreover, the number of subjects who underwent exercise echocardiography was small, and this needs further study. Although the physiological principles of the torsion–displacement loop seem sound, it would be optimal to further validate this relatively new index in animal and human studies to characterize its response to positive and negative inotropy, to increased heart rate (eg, pacing), and to preload and afterload modulation. The sensitivity, specificity, and test characteristics to detect graft dysfunction, in general, and graft rejection specifically, are still undetermined, and it is unknown how often the torsion–displacement loop should be assessed in the individual patient. The intraobserver and interobserver variability reported in the study seem adequate but are provided only for assessment of basal and apical rotation and not for assessment of the torsion–displacement loop, especially its systolic slope. The reliability of this measure is important if it is to be used in clinical practice.

Nonetheless, given the potential advantages reviewed earlier, the study by Nawyouth and colleagues15 provides strong impetus to further investigate echo-derived rotation mechanics, force–volume relations, ventricular work, systolic–diastolic coupling, and response to exercise in children with potential or apparent ventricular dysfunction, including OHT. Using myocardial mechanics to derive myocardial work and its response to exercise hold potential to detect intrinsic myocardial dysfunction, for example, in OHT graft dysfunction. These should also be valuable to detect inadequate ventricular response to increased loading that occurs in many other conditions. Going forward, 3D echo can simultaneously assess torsion and LV volumes, obviating the need to use surrogates for volume (displacement in this case). Moreover, assessment of torsion by 3D echocardiography, assuming adequate volume rates, should also be more reliable, in that basal and apical rotation are derived simultaneously, rather than from separate clips at potentially different heart rates.

Finally, whenever a new index is proposed, we should be cognizant, as pertinently stated in the recent summary of the 2015 International Paediatric Heart Failure Summit,19 that while echocardiography has a central role in diagnosing and characterizing ventricular dysfunction, there is a profusion of available measurements. Consequently, it can be difficult for the clinician to decide which measurements to make, how to make them, and what these measurements actually mean for the patient.19 Although noninvasive assessment of ventricular force–volume relations and work and their response to exercise seem germane to detect OHT graft dysfunction, these entail equipment, time, and expertise. They may ultimately be worthwhile; but it is incumbent on us as a community to build on innovative research, such as that of Nawyouth et al, to determine which parameters are clinically relevant and provide added value in the assessment of pediatric ventricular dysfunction, in general, and OHT graft dysfunction, specifically.


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